REMARKS

Claims 40-44 are currently pending. Claims 1-39 are cancelled without prejudice. Claims 40-44 are new, and are supported by the original claims and the specification, particularly at paragraphs 2, 5, 31, and 36. The new claims add no new matter.

The Examiner has rejected claims 27-39 under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. The Examiner has rejected claims 35-39 under 35 U.S.C. § 112, first paragraph, as being unenabled. The Examiner has rejected claims 27-34, 36 and 37 under 35 U.S.C. § 112, second paragraph, as being indefinite. The Examiner has rejected claims 27-39 under 35 U.S.C. § 101 as directed toward non-statutory subject matter. The Examiner has rejected claims 19-20 and 22-23 under 35 U.S.C. § 103(a) as obvious over Meacham et al. (Meacham et al., 1999, The Hdj-2/Hsc70 chaperones pair facilitates early steps in CFTR biogenesis, EMBO J. 18(6): 1495-1505) ("Meacham et al.") in view of Robbins et al. (U.S. Patent No. 6,881,825 filed August 31, 2000) ("Robbins et al."). For the reasons detailed below, the rejections should be withdrawn and not applied to the new claims, and the claims should be allowed to issue.

I. The Claims Comply With The Written Description Requirement

The Examiner has rejected claims 27-39 under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. The Examiner contends that the claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

The Examiner alleges that the claims are directed to a genus of Cystic Fibrosis Trans-membrane conductance Regulator (CFTR) polypeptide molecules comprising amino acid sequences capable of binding to a molecular chaperone and enhancing CFTR channel activity in any cell expressing any mutant CFTR with no defined structure of the CFTR polypeptide, cell type where expressed, or type/specificity of the mutation. The Examiner further alleges that the specification discloses a single CFTR polypeptide, and does not describe the structure and/or function of all CFTR polypeptides of the genus having the desired characteristics. Additionally, according to the Examiner, the specification does not describe a base sequence of the CFTR polypeptide, rendering the recitation in the claims of deleted amino acid 508 unclear since various CFTR clones exist which may have different sequences and sequence numbering. The Examiner contends that the disclosure of a single CFTR polypeptide is not representative of the entire genus, and therefore alleges that the inventors did not have possession of the invention as claimed.

Applicants submit that the presently submitted new claims address the basis of the Examiner's rejection. The amended claims are directed to a polypeptide comprising a human nucleotide binding domain 1 (NBD1) domain of CFTR in which the amino acid at position 508 has been deleted relative to the entire human CFTR protein. The human CFTR NBD1 domain is known in the art, and the 508 deletion mutation falls within the NBD1 domain (*see* Sheppard et al., 1999, Structure and function of the CFTR chloride channel, Physiol. Rev 79:S23-45; and paragraph 36 of the specification) ("Sheppherd et al."). Additionally, as conceded by the Examiner, the specification describes a human CFTR polypeptide linked to an internalizing peptide that is capable of binding cytoplasmic chaperones and enhancing CFTR channel activity in a cell expressing a mutant CFTR comprising the 508 deletion (page 3 of the Final Office

Action). Furthermore, Applicants assert that the specification discloses a human CFTR polypeptide comprising the human NBD1 domain and the 508 deletion mutation (pages 10-11, paragraphs 36-37). Accordingly, the claimed invention is adequately supported by the written description. Applicants therefore respectfully request that the rejection be withdrawn and/or not applied to the new claims.

II. The Claims are Enabled

The Examiner has rejected claims 27-34 under 35 U.S.C. § 112, first paragraph, as being unenabled. The Examiner states that the specification "does not reasonably provide enablement for any Cystic Fibrosis Trans-membrane conductance Regulator (CFTR) polypeptide molecules comprising amino acid sequences capable of binding to any molecular chaperone and enhance CFTR channel activity in any cell type expressing any mutant CFTR with no defined structure of the CFTR polypeptide, cell type where expressed or type/specificity of the mutation."

Applicants assert that the new claims address the basis of the Examiner's rejection. The new claims are directed to a polypeptide comprising the human NBD1 CFTR domain wherein the amino acid at position 508 numbered relative to the entire human CFTR protein is deleted, not any CFTR polypeptide, as alleged by the Examiner. Applicants submit that Examples 6, 6.1.5 and 7.3 (paragraphs 66, 75-80 and 91 of the specification, respectively), describe a polypeptide comprising the human NBD1 and R domains along with the 508 deletion linked to an internalizing peptide wherein application of the polypeptide to cells expressing mutant CFTR was able to increase CFTR channel activity in the cells. Further, the Examiner concedes that the disclosure is enabling for a CFTR polypeptide comprising human CFTR and

the 508 deletion as well as an internalizing peptide that enhances CFTR channel activity in cells expressing Δ508 mutant CFTR (page 4 and 5 of the Final Office Action). A skilled artisan would not require undue experimentation to introduce the claimed polypeptide into a cell expressing a mutant CFTR protein to enhance CFTR channel activity, as presently claimed. Applicants assert that the claims are enabled by the specification, and respectfully request that the rejection be withdrawn and/or not applied to the new claims.

III. The Claims are Definite

The Examiner has rejected Claims 27-34, 36 and 37 under 35 U.S.C. § 112, second paragraph, as indefinite. The Examiner alleges that the claims fail to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. According to the Examiner, the claims recite CFTR polypeptide sequences with no reference sequences or the recitation of specific sequence identifiers. The Examiner therefore contends that the claims are unclear and indefinite.

Applicants assert that the new claims address the basis for the rejection. As described above, the new claims are directed to an isolated polypeptide comprising the human NBD1 CFTR domain in which the amino acid at position 508 has been deleted relative to the entire human CFTR protein, a protein which had been characterized and known in the art. The human CFTR NBD1 domain comprising the 508 deletion is disclosed in the specification at paragraphs 36 and 37, as well as in the descriptive examples (paragraphs 66, 75-80 and 91). Accordingly, the new claims are definite so that the rejection should be withdrawn and/or not applied to the new claims.

IV. The Claims are Directed to Statutory Subject Matter

The Examiner has rejected Claims 27-39 under 35 U.S.C. § 101 as directed toward non-statutory subject matter. The Examiner contends that the claims read upon naturally occurring proteins and/or nucleic acids, which is non-statutory subject matter. Applicants have amended the claims to recite "An isolated polypeptide comprising ..." as suggested by the Examiner. Thus, Applicants request that the rejection be withdrawn and/or not applied to the new claims.

V. The Claims are Not Obvious

The Examiner has rejected Claims 19-20 and 22-23 under 35 U.S.C. § 103(a) as obvious over Meacham et al. in view of Robbins et al. According to the Examiner, Meacham et al. discloses a CFTR polypeptide comprising two membrane-spanning domains, two nucleotide binding domains, and a regulatory domain that binds the chaperones Hdj-2 and Hsc70. The Examiner further contends that Meacham et al. describes a CFTR polypeptide comprising the Δ508 mutation that binds the chaperones Hdj-2 and Hsc70, and that the earliest stage in which the chaperones can bind CFTR polypeptide intermediates coincides with the translation of the NBD1 domain in the cytosol. The Examiner also contends that Robbins et al. describes internalizing peptides that can facilitate uptake and transport into the cytoplasm of a cell, both *in vivo* and *in vitro*, and that the internalizing peptides include those defined by SEQ ID NOS: 1-3 of the instant application. The Examiner alleges that it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Meacham et al. and Robbins et al. to more efficiently express the CFTR polypeptides of Meacham et al. by incorporating the internalizing peptides of Robbins et al.

Applicants respectfully traverse the rejection, and submit that the presently amended claims are not obvious over Meacham et al. or Robbins et al. considered separately or in combination. To establish a *prima facie* case of obviousness, all the claim limitations must be taught or suggested by the prior art (*In re Royka*, 490 F.2d 981, 180 U.S.P.Q. 580 (C.C.P.A. 1974). *In re Wilson*, 424 F.2d 1382, 1385, 165 U.S.P.Q. 494,496 (C.C.P.A. 1970) states that "All words in a claim must be considered in judging the patentability of that claim against the prior art." The Examiner must also meet three criteria. The Examiner must establish that (1) there is some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings; (2) there is a reasonable expectation of success; and (3) the prior art reference (or references when combined) teach or suggest all the claim limitations. See M.P.E.P. §§ 706.02(j) and 2143. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, rather than Applicants' disclosure.

Applicants submit that the claims are not rendered obvious by the cited references because there is no motivation to combine the references and even if they were combined, the combined teaching of the references neither suggests the claimed invention nor provides a reasonable expectation of success. Although Meacham et al. discloses that NBD1 is needed to bind the chaperones Hdj-2 and Hsc70, and that the 508 deletion mutation increases binding to the chaperones, the polypeptides used by Meacham et al. differ from the polypeptides encompassed by the presently amended claims. The polypeptides disclosed by Meacham et al. comprise the MSD1 domain of CFTR as well as the NBD1 domain (page 1496, column 1, 3rd full paragraph continuing to column 2). Additionally, as stated by the Examiner, Meacham et al. describes that

"the earliest stage at which Hdj-2 and Hsp70 could bind CFTR translation intermediates coincided with the expression of NBD1 in the cytosol" (page 8 of the Final Office Action). Because the MSD1 domain is translated before the NBD1 domain, the translation intermediates disclosed by Meacham et al. that bind the chaperones will necessarily comprise the MSD1 domain. Meacham et al. discloses that the native conformation of a protein is achieved through sequential sub-domain folding events, and that the MSD1 domain of CFTR initiates the first such folding event, followed by the interaction of NBD1 with the chaperones (page 1492, column 1; page 1501, column 1). Meacham et al. hypothesizes that the NBD1-chaperone interaction may be a transient event necessary to stabilize NBD1 until the R domain is translated and available to participate in additional sub-domain interactions with NBD1 (page 1501, columns 1 and 2). As establishing conformational structure proceeds through sequential sub-domain folding events, it would not be obvious to one skilled in the art that the NBD1-chaperone interaction would occur without the presence of the MSD1 domain and the proper execution of the preceding MSD1 sub-domain folding event.

Furthermore, Meacham et al. examined chaperone binding capabilities of CFTR polypeptides endogenously translated from introduced CFTR-encoding nucleic acid molecules. Meacham et al. observed heightened chaperone binding when the CFTR polypeptide comprised the first two domains, MSD1 and NBD1, of CFTR as compared to MSD1 alone or MSD1 and NBD1 in combination with other CFTR domains. Because the sub-domains initiate sequential sub-domain folding events, and earlier events may have consequential affects on subsequent events, such as, for example, the NBD1-chaperone interaction, it would not have been obvious to a skilled artisan that an exogenously administered polypeptide comprising the NBD1 domain and the 508 mutation, in the absence of MSD1, would successfully translocate to the ER and out

compete endogenous CFTR protein for chaperone binding sites. As Meacham et. al. appears to be directed toward elucidating the mechanism of CFTR folding, there would have been no motivation to combine this reference with Robbins et. al.

Applicants assert that the enhancement of CFTR channel activity by the claimed CFTR polypeptide is an unexpected result that could not have been predicted by the combination of Meacham et al. and Robbins et al. Although Meacham et al. discloses the binding of CFTR polypeptides to chaperones, Meacham et al. does not teach or suggest an increase in CFTR channel activity. At most, if, for the sake of argument, Meacham et al. and Robbins et al. were combined, the expected result would be that the internalized peptides would engage in chaperone-mediated folding. The increase in CFTR channel activity is an unexpected consequence resulting from the use of the CFTR polypeptides encompassed by the presently amended claims.

For the reasons set forth above, Applicants believe the presently amended claims are not obvious in view of Meacham et al. or Robbins et al. considered separately or in combination. Thus, Applicants request the rejection be removed and/or not applied to the new claims.

VI. CONCLUSION

Entry of the foregoing amendments and remarks into the file of the above-identified application is respectfully requested. Applicants believe that the invention described and defined by new claims 40-44 are in condition for allowance. Withdrawal of all rejections and reconsideration of the amended claims is requested. An early allowance is earnestly sought.

Respectfully submitted,

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Enclosures